



Armed Forces College of Medicine

AFCM



Rheumatic fever: An immunological insight

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INTENDED LEARNING OBJECTIVES (ILO)



- **By the end of this session the student will be able to:**
 - 1. Outline the aetiology of rheumatic fever**
 - 2. Describe the pathogenesis of the disease**
 - 3. List the important lesions and clinical manifestations**
 - 4. Define the important diagnostic features & lab findings in rheumatic fever**

Definitions

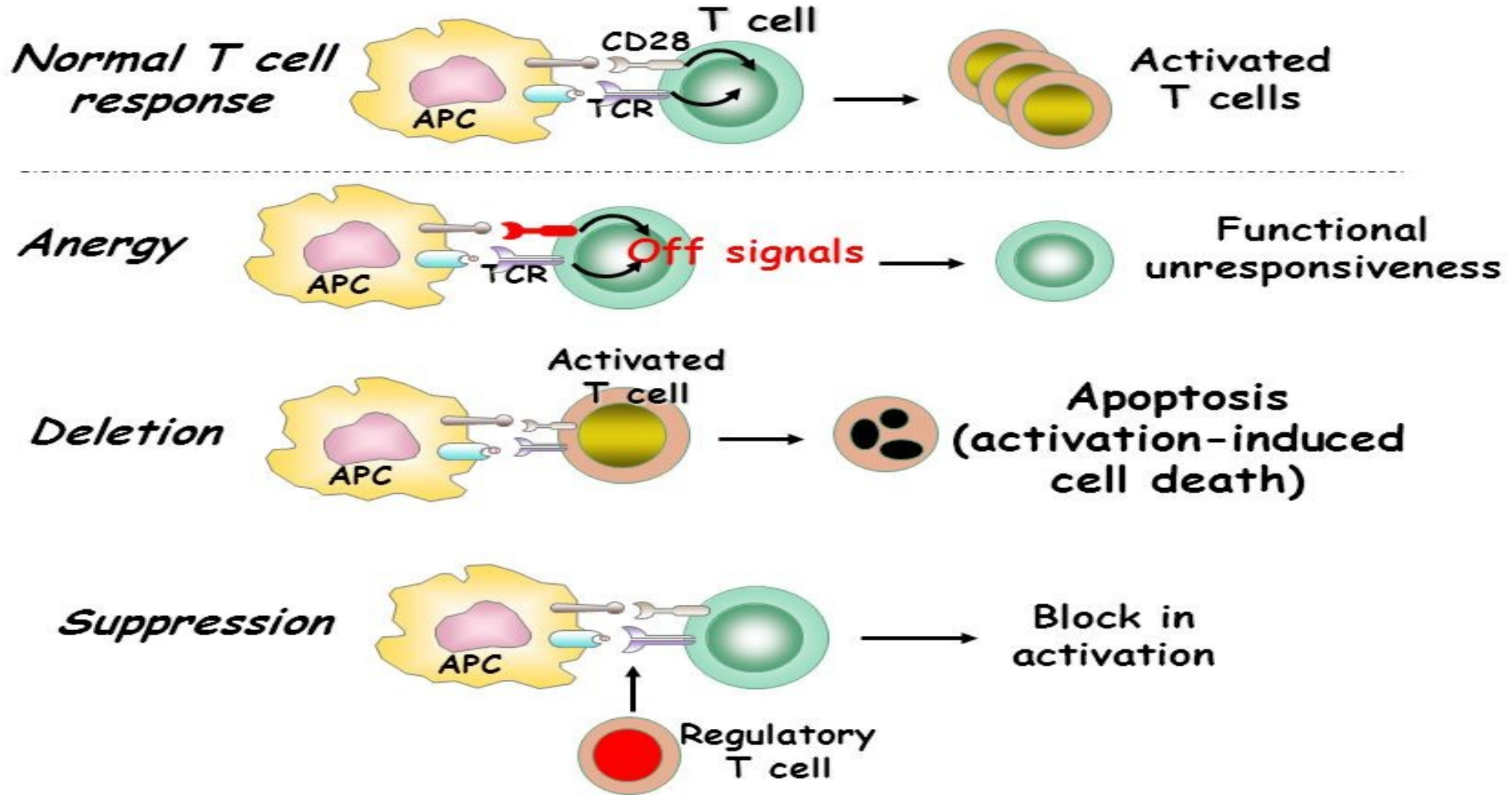


- **Autoimmune disease:** Adaptive IR attacking own body tissues

Occurs due to failure of tolerance

- **Heterophil Antigen**
- **Molecular Mimicry**
- **Central & Peripheral tolerance**

Peripheral tolerance



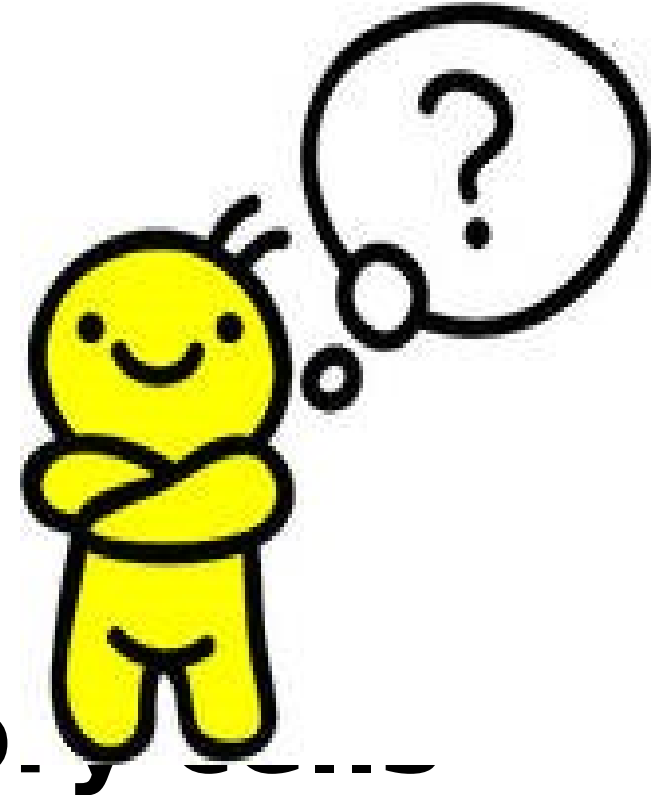
In a nut shell ☐

- **Immune tolerance:**

Central: Clonal deletion/ receptor editing

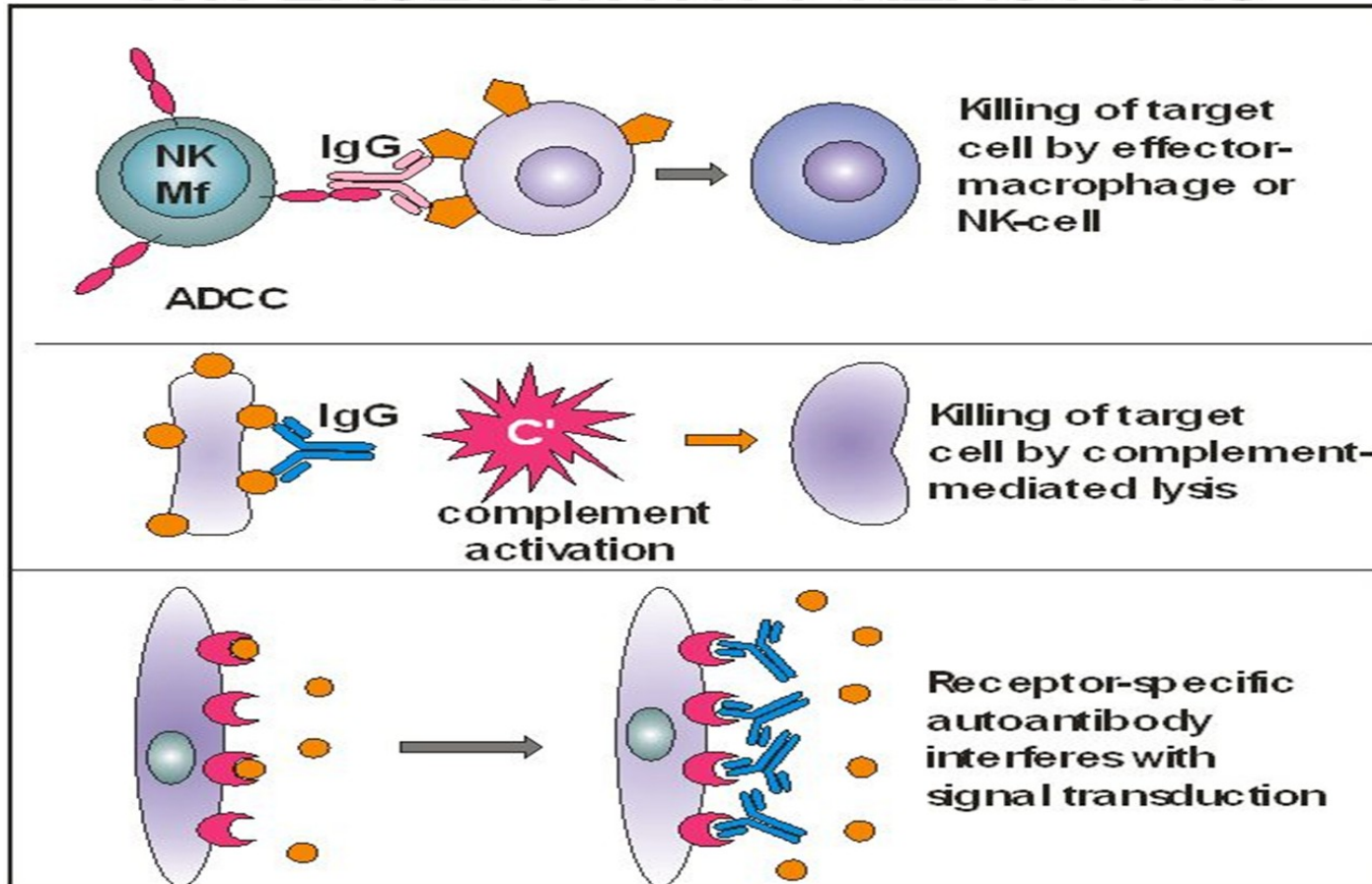
Peripheral:

- ✓ **Clonal anergy**
- ✓ **Clonal ignorance**
- ✓ **Deletion**
- ✓ **Suppression by T regulatory cells**



Type II Hypersensitivity reactions

MECHANISMS OF TYPE II HYPERSENSITIVITY REACTIONS



Quiz



- Which of the following organisms is involved in the pathogenesis of rheumatic fever?
 - Streptococcus pyogenes*
 - Streptococcus agalactiae*
 - Staphylococcus aureus*
 - Streptococcus pneumoniae*
 - Staphylococcus epidermidis*

Type II Hypersensitivity reactions



Rheumatic Fever

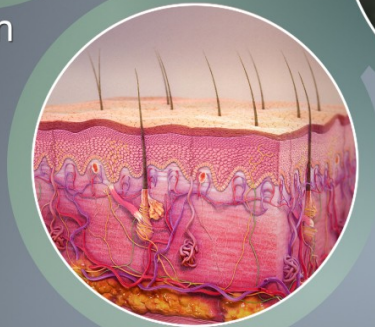
An inflammatory disease that can affect



Brain



Heart

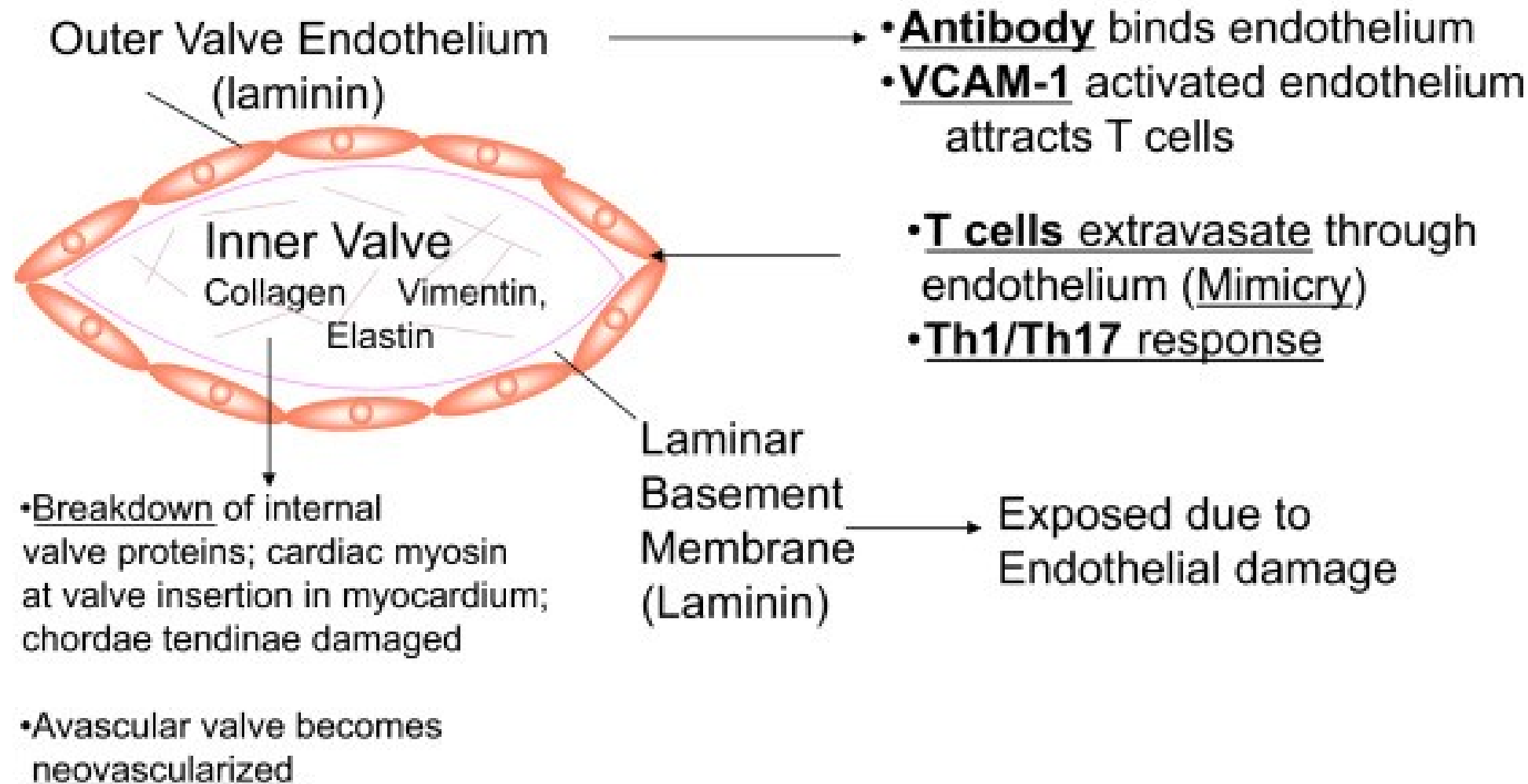


Skin



Joints

Rheumatic Heart Disease Valve Model



Molecular Mimicry

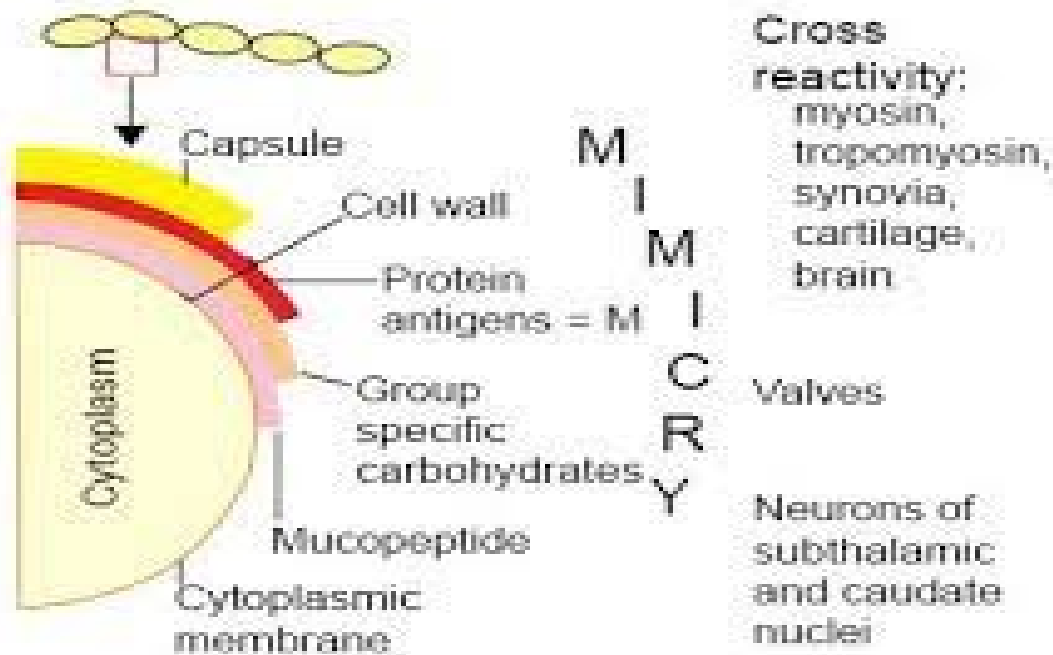
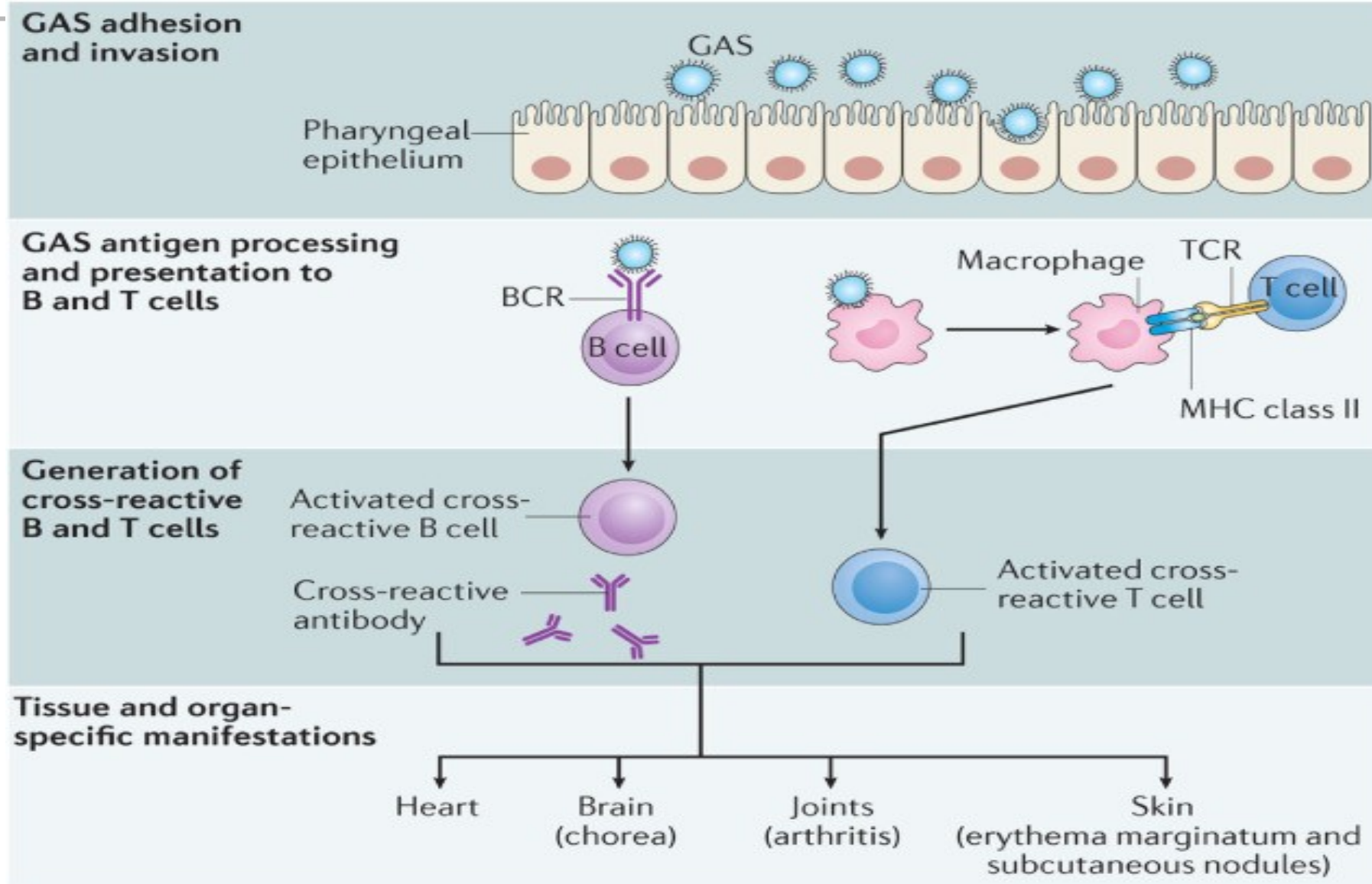


Fig. 4 : Diagram showing Molecular Mimicry in Acute Rheumatic Fever. Similarity between streptococcal cell wall antigens with endogenous antigens in cardiac tissue, synovium, cartilage and brain leads to immunologic attack by the host antibodies and manifestations of acute rheumatic fever.



- ***Heterophile antigens*** are a group of similar antigens found in unrelated animals, IE, man, sheep, horse, dog cat, mouse.
- ***Heterophile antibodies*** produced against heterophile antigens of one species will cross react with others.

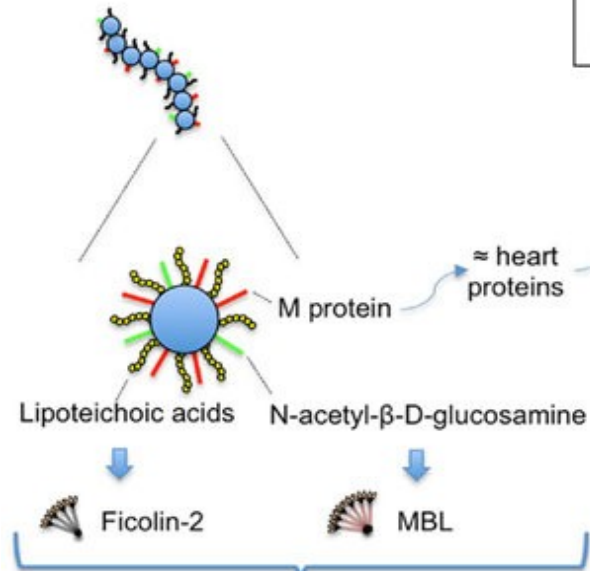
Molecular mimicry



Mechanism of tissue damage



Streptococcus pyogenes



Complement activation and phagocytosis

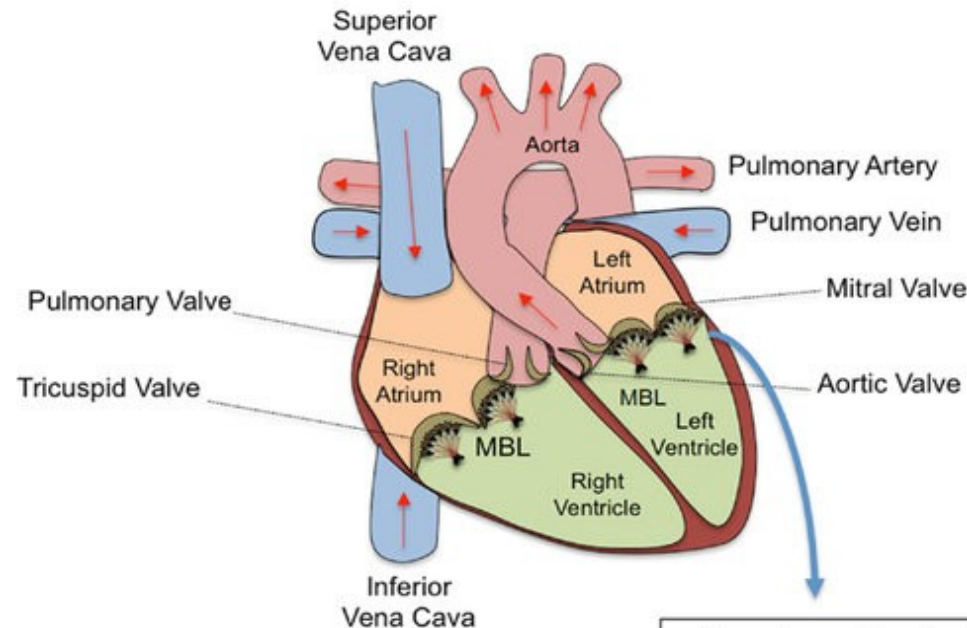
Proteins
High MBL levels
Low Ficolin-2 levels

Genetic Polymorphisms
MBL2
FCN2

Autoimmunity

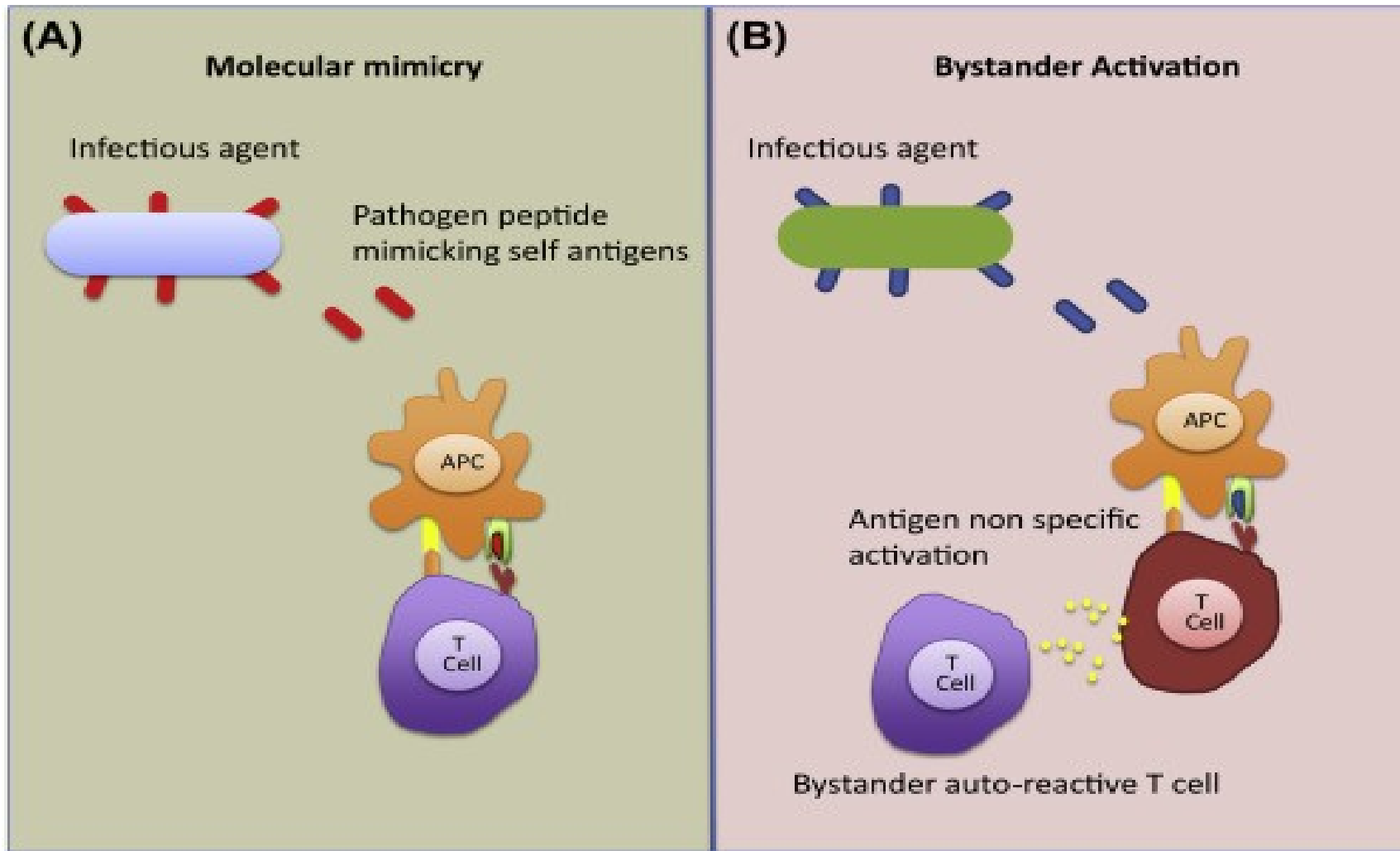
\approx heart proteins

Rheumatic Heart Disease



Complement activation and inflammation

Molecular mimicry Vs Bystander activation





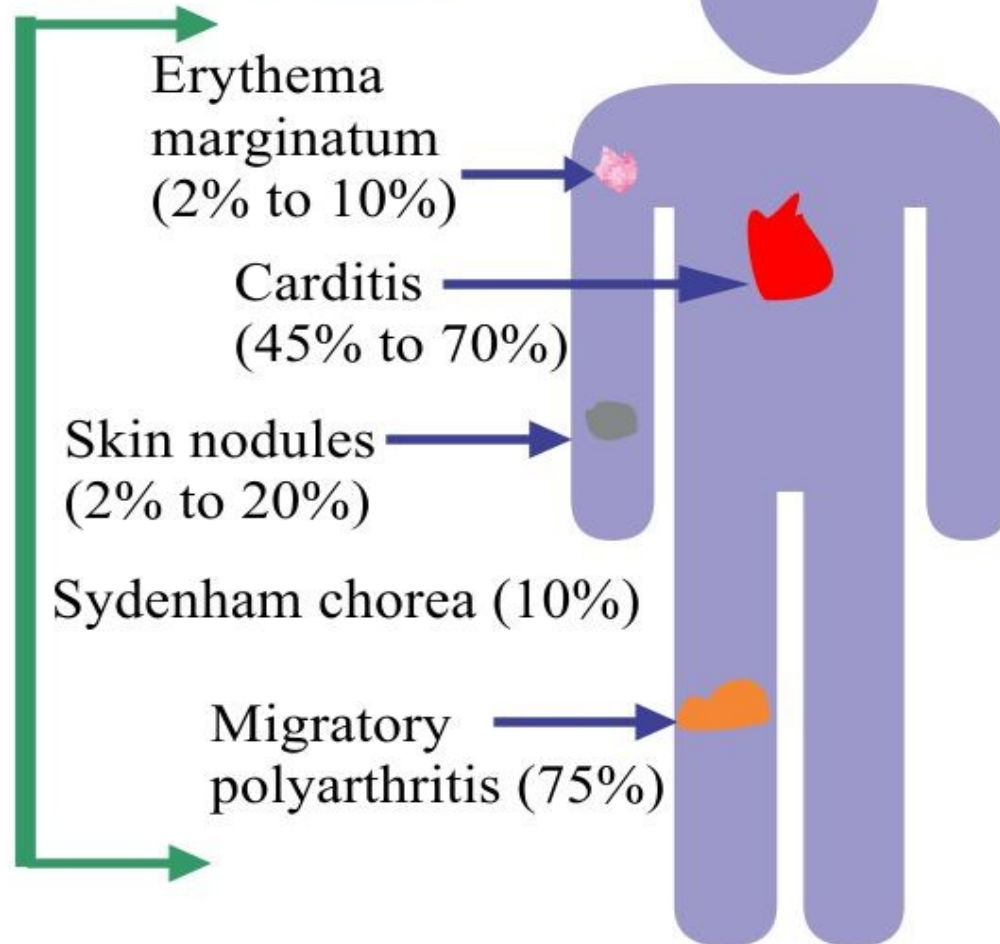
Signs & Symptoms




Diagnosis



Major criteria



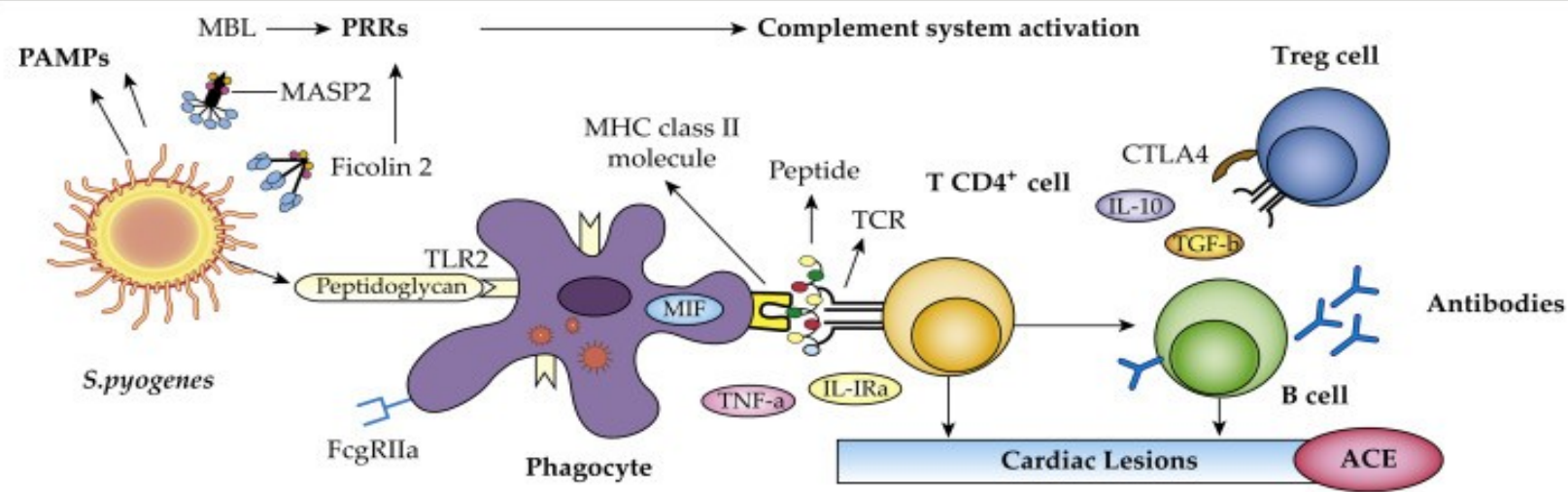
Minor criteria

- 
1. Fever
 2. Arthralgia
 3. Raised ESR
 4. Raised CRP
 5. Prolonged PR-interval
 6. H/O Rheumatic fever or Rheumatic heart disease

Immunological mediators role in Rheumatoid fever



Immune Response against *Streptococcus pyogenes*



Genes and their role

Pathogen Recognition and Complement System Activation

MBL2 - recognizes mannose and N-acetylglucosamine in pathogens
MASP2 - protease; lectin pathway
FCN2 - codifies Ficolin 2; carbohydrate binding; opsonic activities

Pathogen Recognition and Phagocytosis

TLR2 - pathogen recognition (lipoproteins); activation of innate immunity
FCGRIIa - phagocytosis and clearing of immune complexes
MIF - macrophage migration inhibitory factor; macrophage function

Antigen presentation to T cells

HLA-DRBI, *HLA-DQAI*, *HLA-DQBI* - presenting peptides derived from extracellular proteins

Proinflammatory Cytokines

TNFA - proinflammatory cytokine
IL-1RA - inhibits the IL-1 function ; IL-1 inflammatory responses

Immune Response Control

CTLA4 - inhibitory signal to T cells
IL-10 - immunoregulation
TGFB1 - regulates cell proliferation, differentiation, migration

Cardiac Tissue Damage Progression

ACE - enzyme; conversion of angiotensin I into a physiologically active peptide angiotensin II.

Quiz



Which of the following represent the main mechanism of tissue damage in Rheumatic fever?

- a. cross-reactivity of pathogen and self antigens.**
- b. expression of self antigen in the thymus or bone marrow.**
- c. low avidity presentation of some self peptides in the thymus.**
- d. random generation of TCR and BCR specificities.**
- e. tissue injury which releases normally hidden self antigens.**

Diagnosis of Rheumatic



fever

- Rheumatic fever is mainly a clinical diagnosis
- *No single diagnostic sign or specific laboratory test available for diagnosis*
- Diagnosis based on **MODIFIED JONES CRITERIA**

- ✓ Jones Criteria – Diagnosis of ARF requires **2 major criteria OR one major and two minor criteria** + evidence of recent streptococcal infection

Laboratory findings



❑ Throat culture

- ◊ Throat culture findings for group A beta hemolytic *Streptococcus* are usually negative by the time symptoms of rheumatic fever or rheumatic heart disease appear.

❑ Rapid antigen detection test

- ◊ This test allows rapid detection of group A streptococcal antigen and allows the diagnosis of streptococcal pharyngitis and the initiation of antibiotic therapy while the patient is still in the physician's office.

Laboratory findings



Antistreptolysin O titer (ASO)

Positive titre: >200 IU/mL

- Detects antibody to the antigen streptolysin O produced by group A streptococci. Titer rises to a peak at 4-6 weeks and may remain elevated for 1 year.

Positive in:

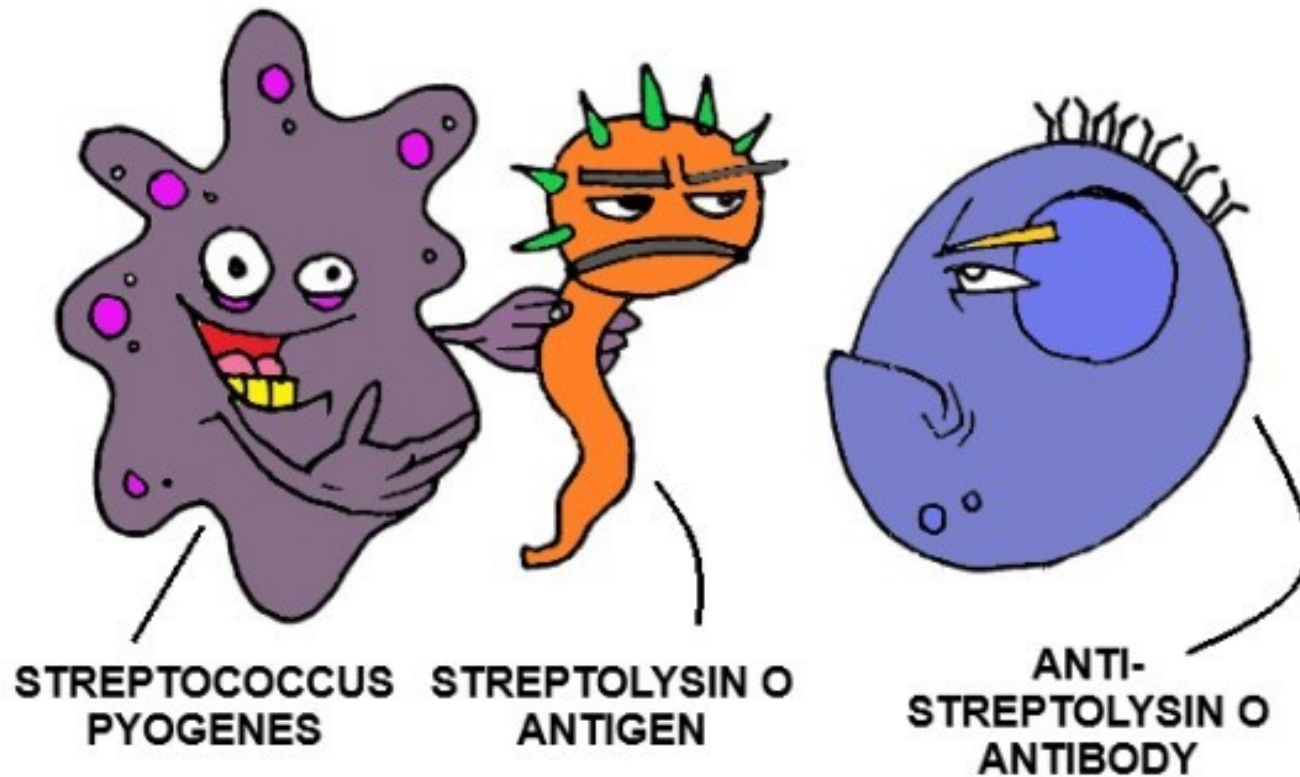
- Streptococcal infection (eg, upper airway infections, scarlet fever)
- post-streptococcal infection complication (eg, glomerulonephritis and rheumatic fever).

False positive in

- Some bacterial infections.



Laboratory findings



Quiz



Which of the following denotes a laboratory finding in Rheumatic fever supporting the diagnosis?

- a) Chorea**
- b) Positive anti-streptolysin O titer**
- c) PCR**
- d) Prozone phenomenon**
- e) Throat culture**

SUGGESTED TEXTBOOKS



- 1. Review of Medical Microbiology and Immunology, Warren Levinson Chapter 66 p. 1214: 1231***
- 2. Cellular and molecular Immunology , Abul Abbas & Lichtmann Chapter 15 p.315:335***

THANK

YOU